PHARMACOLOGY

BHARATHIDASAN UNIVERSITY

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Programme: M.Sc., Biomedical Science

Course Title : Pharmacology and Toxicology
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Unit-I
General Pharmacology Part-3

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THERAPEUTIC WINDOW PHENOMENON

- Optimal therapeutic effect is exerted only over a narrow range of plasma drug concentrations or drug doses;
- both below and above this range, beneficial effects are suboptimal,
- Tricyclics (imipramine etc.) plasma concentration is maintained between 50-150 ng/ mL.

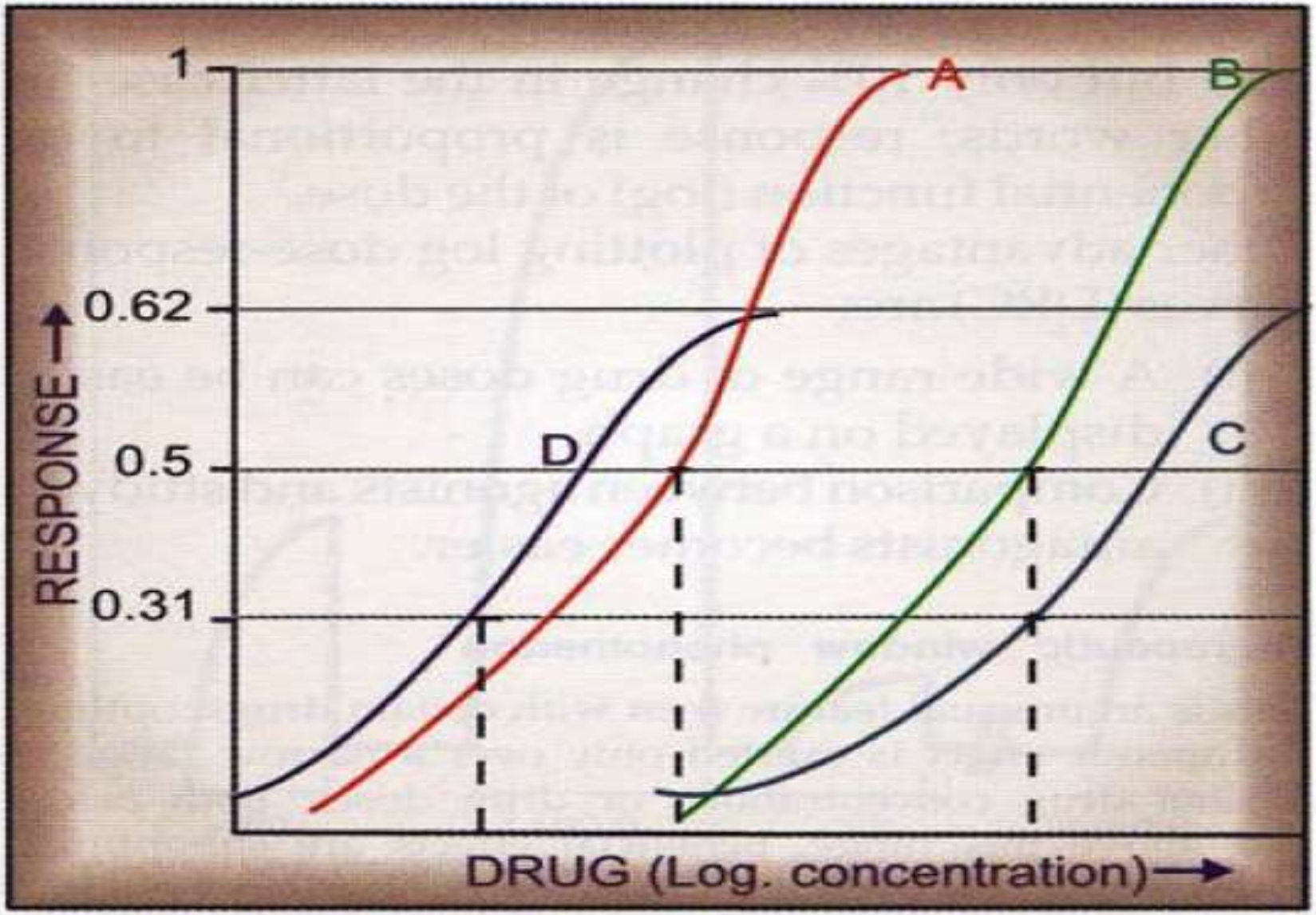


Fig. 4.12: Illustration of drug potency and drug efficacy. Dose-response curve of four drugs producing the same qualitative effect

- Potency is an expression of the activity of a drug in terms of the concentration or amount of the drug required to produce a defined effect, whereas clinical efficacy judges the therapeutic effectiveness of the drug in humans.

COMBINED EFFECT OF DRUGS

- When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit synergism or antagonism.
- SYNERGISM-When the action of one drug is facilitated or increased by the other, they are said to be synergistic.
- Additive:

  Effect of drugs A + B = effect of drug A + drug B
- Supraadditive:

  Effect of drug A+ B > effect of drug A+ drug B

ANTAGONISM

Effect of drugs A+ B < effect of drug A +drug B

Physical

Chemical

Physiological

Receptor

DRUG DOSAGE

- 'Dose' is the appropriate amount of a drug needed to produce a certain degree of response in a patient.
- Standard dose
- Regulated dose
- Target level dose
- Titrated dose

BODY SIZE

$$\text{Individual dose} = \frac{\text{BW (kg)}}{70} \times \text{average adult dose}$$

It has been argued that body surface area (BSA) provides a more accurate basis for dose calculation, because total body water, extracellular fluid volume and metabolic activity are better paralleled by BSA.

$$\text{Individual dose} = \frac{\text{BSA (m}^2\text{)}}{1.7} \times \text{average adult dose}$$

The BSA of an individual can be calculated from Dubois formula:

$$\text{BSA (m}^2\text{)} = \text{BW (kg)}^{0.425} \times \text{Height (cm)}^{0.725} \times 0.007184$$

AGE

2. Age The dose of a drug for *children* is often calculated from the adult dose

$$\text{Child dose} = \frac{\text{Age}}{\text{Age} + 12} \times \text{adult dose} \quad \text{... (Young's formula)}$$

$$\text{Child dose} = \frac{\text{Age}}{20} \times \text{adult dose} \quad \text{...(Dilling's formula)}$$

- Hepatic drug metabolizing system is inadequate in newborns --chloramphenicol can produce gray baby syndrome.
- Elderly In the elderly, renal function progressively declines (intact nephron loss) so that g.f.r. is - 75% at 50 years

- Females have smaller body size and require doses that are on the lower side of the range.
- Treatment of heart failure with digoxin is reported to be associated with higher mortality among women than among men.
- Gynaecomastia is a side effect (of Ketoconazole,metoclopramide, chlorpromazine, digitalis) occur only in men.
- Drugs given during pregnancy affect fetus

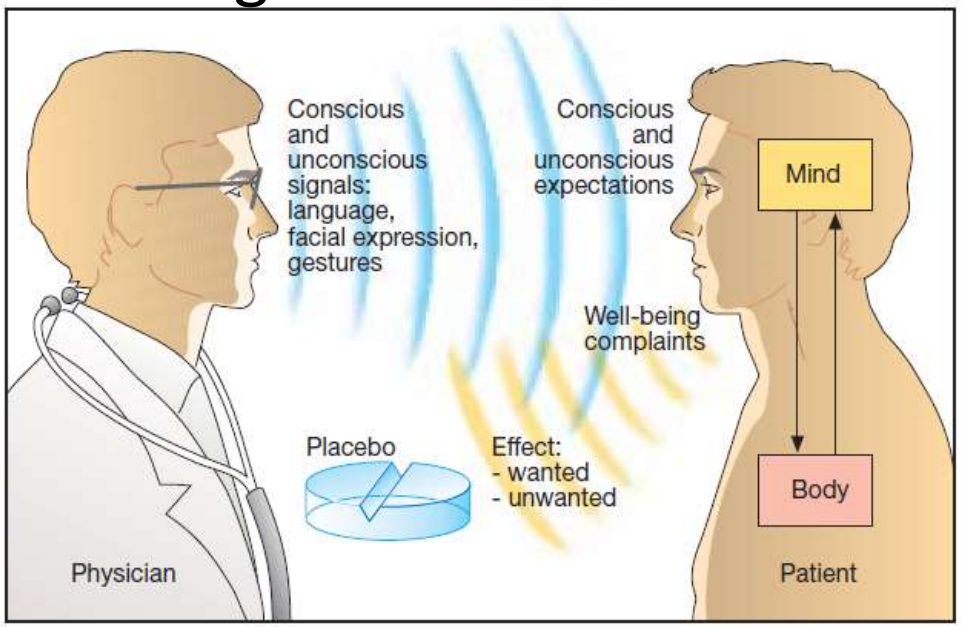
PHARMACOGENETICS AND PHARMACOGENOMICS

- Genetics
- The dose of a drug to produce the same effect may vary by 4-6 fold among different individuals.
- Transporters, Metabolizing enzymes, Ion channels, Receptors with their Couplers and Effectors are controlled genetically

- Route of administration
- Environmental factors and time of administration
- Pathological states

Psychological factor : Efficacy of a drug can be affected by patient's beliefs, attitudes and expectations.

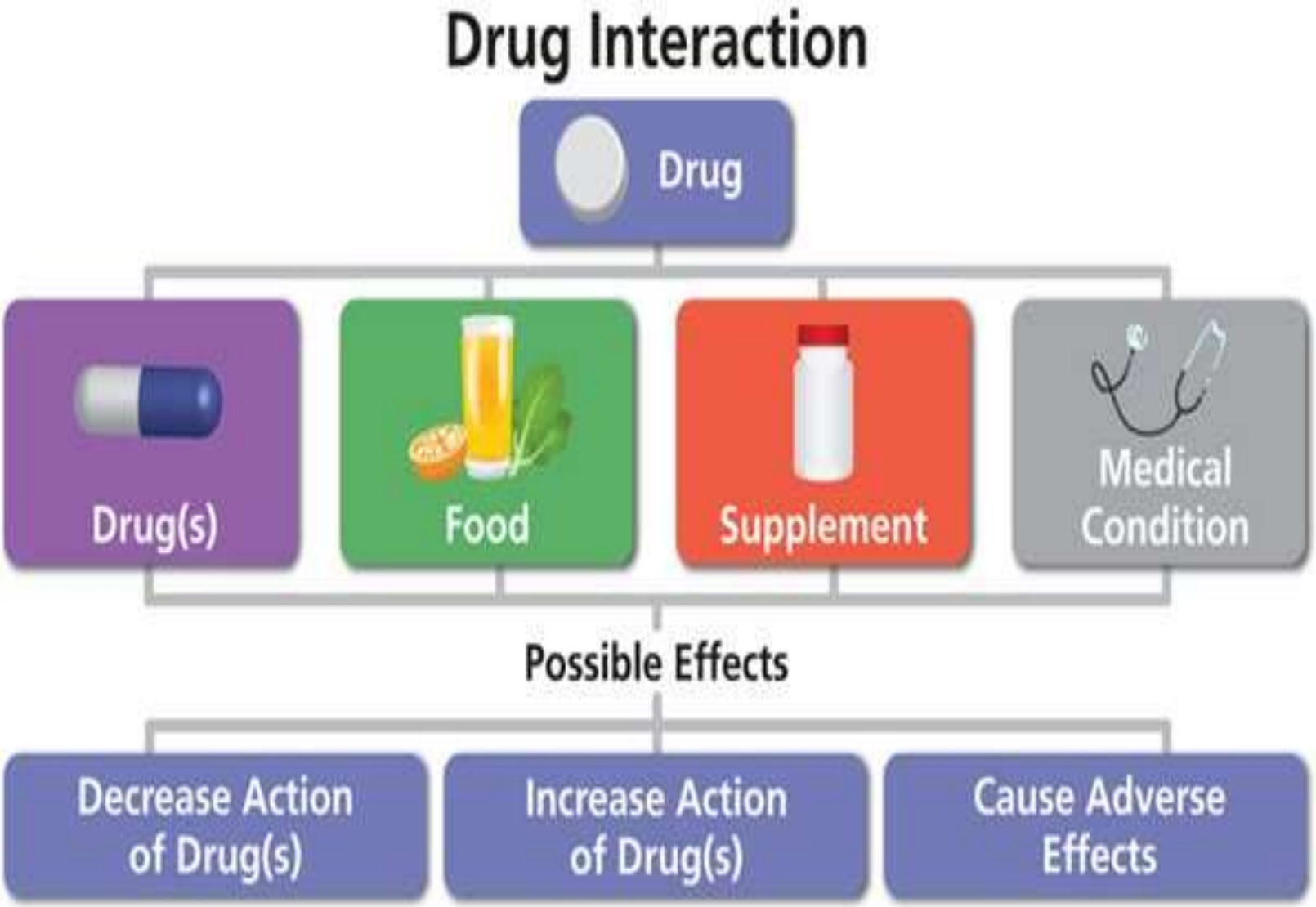
Placebo This is an inert substance which is given in the garb of a medicine. It works by psychological rather than pharmacological means and often produces responses equivalent to the active drug.



- Cumulation: Any drug will cumulate in the body if rate of administration is more than the rate of elimination.
- Tolerance It refers to the requirement of higher dose of a drug to produce a given response
- Cross tolerance It is the development of tolerance To pharmacologically related drugs

  e.g. alcoholics are relatively tolerant to barbiturates and general anaesthetics.

- Tachyphylaxis (Tachy-fast, phylaxis-protection) is rapid development of tolerance when doses of a drug repeated in quick succession result in marked reduction in response.
- Drug resistance It refers to tolerance of microorganisms to inhibitory action of antimicrobials, e.g. Staphylococci to penicillin


Drug Interaction
Drug
Drug(s)
Food
Supplement
Medical Condition
Possible Effects
Decrease Action of Drug(s)
Increase Action of Drug(s)
Cause Adverse Effects

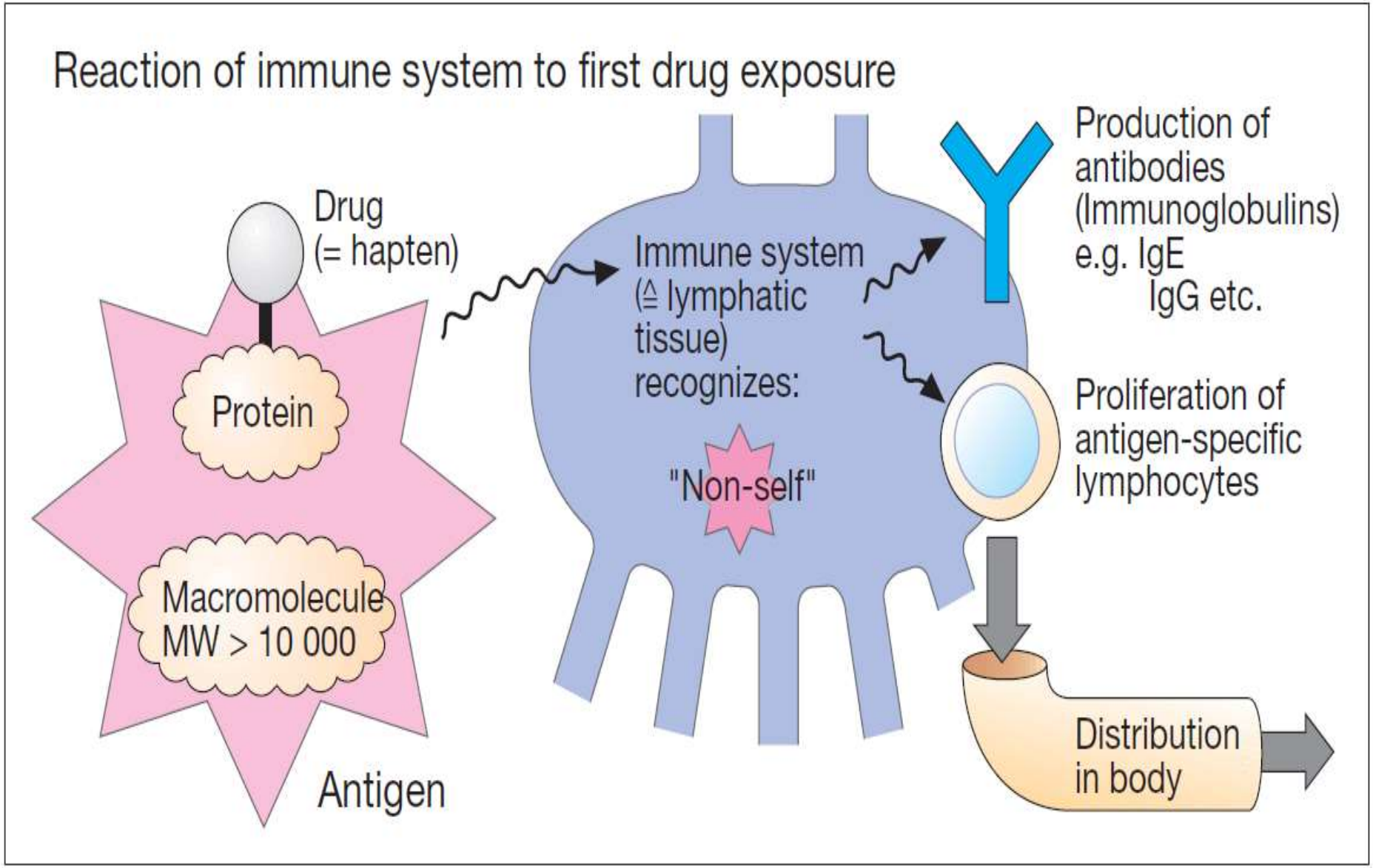
Stages in new drug development

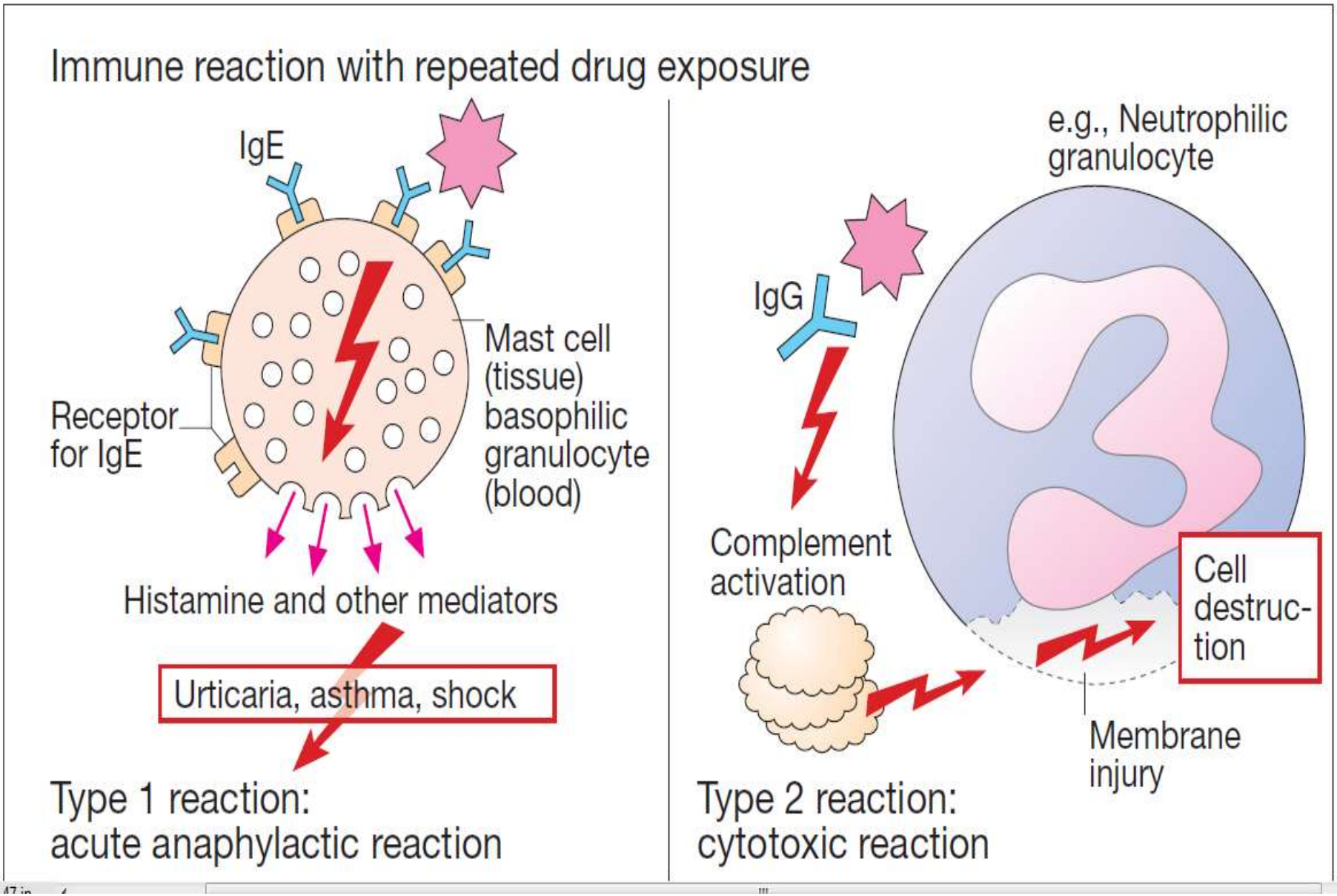
- Synthesis/isolation of the compound: (1–2 years)
- Preclinical studies: screening, evaluation, pharmacokinetic and short-term toxicity testing in animals: (2–4 years)
- Scrutiny and grant of permission for clinical trials: (3–6 months)
- Pharmaceutical formulation, standardization of chemical/biological/immuno-assay of the compound: (0.5–1 year)
- Clinical studies: phase I, phase II, phase III trials; long-term animal toxicity testing: (3–10 years)
- Review and grant of marketing permission: (0.5–2 years)
- Postmarketing surveillance: (phase IV studies)

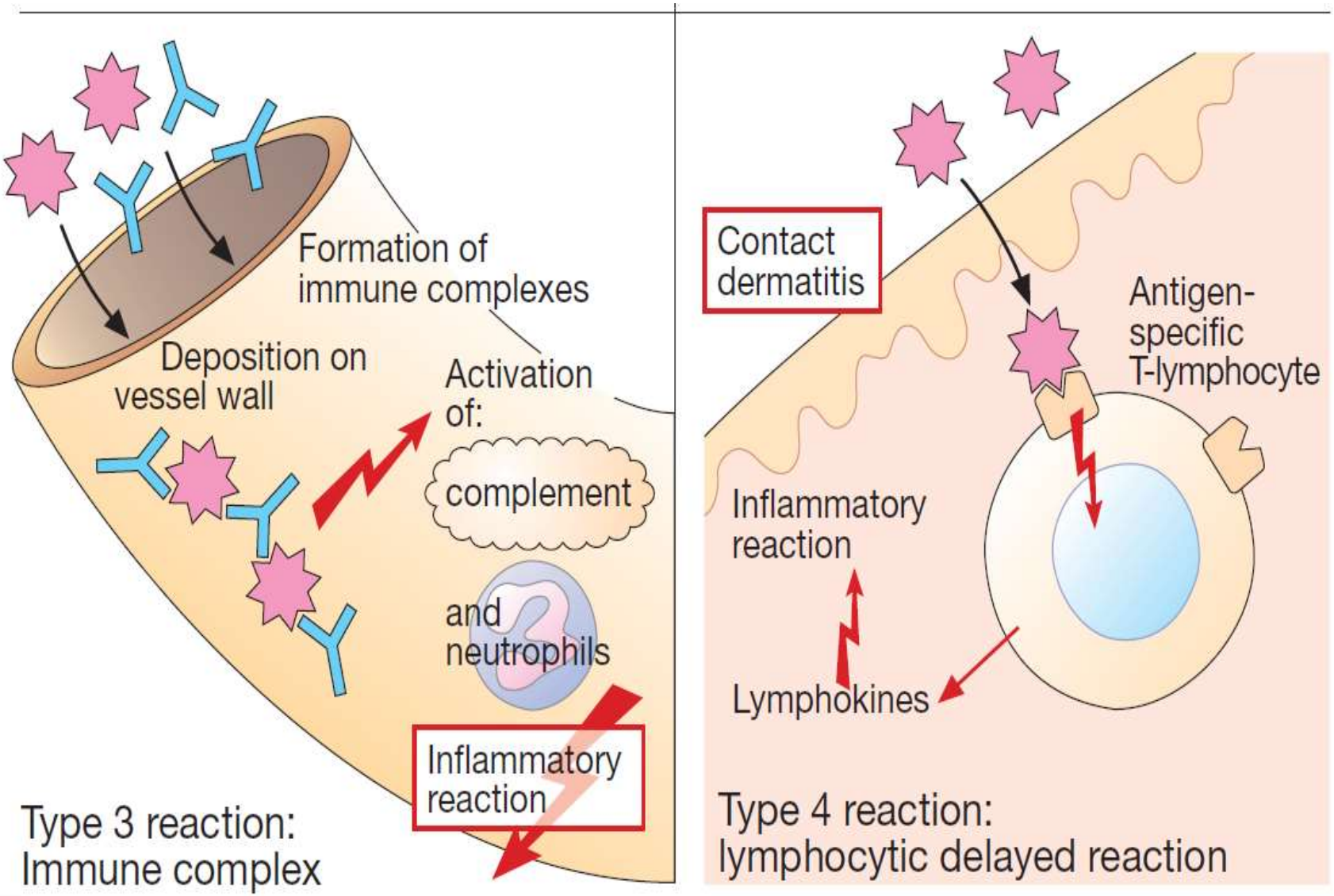
Clinical trials

- Preclinical studies
- Phase I: Human pharmacology and safety
- Phase II: Therapeutic exploration and dose
- Phase lll: Therapeutic confirmation/comparison
- Phase IV: Postmarketing surveillance/studies

- **Type A ADR, augmented (quantitative) ADR,**
- **Largely predictable on** the basis of the known pharmacological actions of a drug and usually are dose related.
- They are extension of the pharmacological effects e.g., insulin hypoglycemia, or an effect due to an action of the drug at another site (e.g., anticholinergic effects of phenothiazines).
- **Type B ADR bizarre (qualitative) ADR.**
- **The symptoms and signs** observed are different from those expected from the known pharmacological actions of the drug and are not dose-related, unpredictable effects.
- Their mechanism is sometimes known (genetic or immunological) but may often be unknown. **Idiosyncrasy is a Type B ADR**


Reaction of immune system to first drug exposure
Drug
(= hapten)
Protein
Macromolecule
MW > 10 000
Antigen
Immune system
(≙ lymphatic
tissue)
recognizes:
"Non-self"
Production of
antibodies
(Immunoglobulins)
e.g. IgE
IgG etc.
Proliferation of
antigen-specific
lymphocytes
Distribution
in body


Immune reaction with repeated drug exposure
IgE
Mast cell (tissue) basophilic granulocyte (blood)
Receptor for IgE
Histamine and other mediators
Urticaria, asthma, shock
Type 1 reaction: acute anaphylactic reaction
e.g., Neutrophilic granulocyte
IgG
Complement activation
Cell destruc-tion
Membrane injury
Type 2 reaction: cytotoxic reaction


Formation of immune complexes
Deposition on vessel wall
Activation of:
complement
and neutrophils
Inflammatory reaction
Type 3 reaction: Immune complex
Contact dermatitis
Antigen-specific T-lymphocyte
Inflammatory reaction
Lymphokines
Type 4 reaction: lymphocytic delayed reaction

Factors which modify drug action

(1) route of administration,

(2) rate and degree of absorption,

(3) rate of elimination,

(4) effect of other drugs,

(5) tolerance,

(6) idiosyncrasy and allergy,

(7) disease.

Acknowledgement

- The Presentation is being used for educational and non commercial Purposes
- Thanks are due to all the original contributors and entities whose pictures were used in the creation of this presentation.